NUTRITION REVIEWS

VOL. 1 AUGUST, 1943 No. 10

FOOD AND WAR

Whether an Army is fighting or not, it must eat. It must be fed regularly and continuously, and on a diet which keeps it fit for any undertaking. The strategy of war may await the availability of other munitions; as, for example, an aerial offensive may well await the development and final delivery of the required airplanes, bombs, gasoline, and other appurtenances. The supply of food, however, is a daily consideration that is related to the size and geographical distribution of the Army in being, regardless of its tactical missions. There can be no interruption in food production, or in the supply lines, regardless of any consideration.

Thus, upon the Quartermaster Corps is placed a very complex problem; it must experiment and at the same time produce completely the food requirements of the Army. Research must be conducted expeditiously on the highest plane of professional performance and yet the results of research must fit harmoniously into established military principles and practices. Production must continue at absolute capacity without interruption even while the preparations for product changes are going forward. What, in peactime mass feeding, would be dismissed as an impossible objective, must be anticipated and solved as a routine operating decision. General Somervell has a motto for the Army Service Forces: "The impossible we do immediately; the miraculous sometimes takes a little longer." In food supply, whether the indicated solution is to achieve either the impossible or the miraculous, perfection must be achieved in advance of the materialized crisis.

Ultimately, wars are lost when either the army in the field or the civilian producers at home are reduced below the subsistence level. If steel and TNT are the sinews of war, then certainly food is its blood stream. An adequate food program in war requires maximum nutritional value in the product combined with maximum effective availability. The former is the field of food research and experimentation, and the latter is the science of logistics. These problems are inextricably joined together.

Some of the problems have been faced and solved. Others are under study, and still others are perhaps unknown. Part of our mission is to anticipate as many of the difficulties as possible, and to have at least the nature of the problem well defined. Some of the early phases we have faced were fundamentally involved in the economic conversion from peace to war, and the impact of that conversion on the food consuming habits of people.

Energy building foods are subject to greatly expanded demand during war. Four factors contribute to this demand, namely: (1) A man eats more as a soldier than he did as a civilian; (2) More of the nation is working at manual tasks than ever before, and during longer hours; (3) The higher level of income prevailing has increased the ability of large groups to enjoy better food than previously; (4) Aid to our Allies and to friendly, distressed nations has, of course, been carried on at an unprecedented scale that is completely familiar to all.

The Army has examined and reexamined its own share of this demand, and by that study has progressively decreased the consumption of food where such reduced consumption is possible. In twenty-three months, the Army has instituted twenty-nine separate major measures to effect

greater conservation. Coffee, tea, fats, canned goods, and butter are among the specific items the consumption of which has been curtailed. It is a mistake to assume that the Army stands aloof from conservation; its demonstrated record is excellent.

The Army has likewise considered it to be in the national welfare to contribute to expanding the available supply, in addition to economizing. This has taken three major forms, namely: (1) Exploitation, in the greatest degree, of surplus crops and items by a timely system of authorizing substitutions in approved menus; (2) Expansion of processing industries to effect a better correlation between agricultural production and distribution; (3) Maximum exploitation of local resources abroad.

Then, of course, we have the problem of transportation, particularly of shipping. Demand for matériel is always infinite in war; no merchant fleet could ever be adequate, for our operations would then expand with every increase in transportation availability. Food offers a fertile field for measures to increase the effectiveness of shipping, and many are now standard practice.

There are two major technics of exploiting space available; namely, reduction of bulk and reduction of stowage space otherwise wasted. The influence of dehydration has already been made obvious. We are now embarked on a program of extending this economy by compression. Having squeezed the water out of a wide variety of products, we shall squeeze the air out of them also. Thus, in some products, two ships now carry in dehydrated food what normally required sixteen ships. Compression will further eliminate one ship, so that one ship will carry in food value what only a short time ago required sixteen.

Likewise, further economies are achieved by revised packaging methods. The package has in the Army lost its merchandising value and must today be adapted strictly to serve its utilitarian function The substitution of a rectangular for a cylindrical container, for example, saves 22 per cent of the normal space required.

Then there are also the specialized problems created by military demands. They have to do with relating feeding to fighting under particular combat conditions. One of the most obvious, but least publicized, is the problem created in the kitchen itself. The kitchens of war are different from those of peace!

Allowance must be made for the probability that foods, perhaps even the same original shipment, will be prepared both in perfectly equipped kitchens in England, and in a water soaked foxhole in New Guinea. Simplicity in preparation, which permits maximum enjoyment and nutrition under both circumstances, is a wartime prerequisite of food products.

Regimentation is required to produce good soldiers; standardization is required to make effective war goods. The problem of emergency diversion of war goods in transit, technical mass production problems, administrative requirements, all reduce the normal variety usually produced for special markets. Were it possible, the ideal in Army food would be products that could be prepared and eaten either at 40° below in Alaska or at 135° above in the South Pacific.

Meeting such a theoretical requirement would embrace the whole realm of food chemistry and the know-how of the industry. Some examples of the problem are: (1) Producing foods that will not be damaged by freezing, and packed in containers that will not rupture under varying temperatures. (2) Preparing fats and oils which are readily usable regardless of temperature. (3) Training in the preparation of frozen and dehydrated foods. (4) Training in the preparation of foods in subfreezing areas, or in high altitudes. (5) Preventing insect and vermin infestation. (6) Reducing the hygroscopic properties

of food (or the container) in humid areas. (7) Reducing the ever-present problem of spoilage, particularly where combat or climatic conditions prevent any kind of prudent storage or protection.

These are vastly different merchandising problems from any which the industry has ever faced before. Our American ingenuity is solving many of them directly, and we are also finding alternative products and methods where a direct solution is not possible. Actually, of course, we cannot produce a one-purpose, all-climate diet. On the other hand, we must always strive for maximum interchangeability. At the same time we must recognize and provide for special nutritional problems created by either the demands of specialized troops, or of terrain, or of geophysical conditions.

This war had been preceded by a considerable amount of mobilization planning. For almost twenty years the Army and Navy had been developing methods of mobilizing the national resources for the time when we would be faced with imminent war. Industry, likewise, for over twenty years has been considerably occupied with research into markets, consumer habits, and products. The nation was better equipped, therefore, to enter this war than any previous one because there were extant major programs of scientific research which, while loosely organized as a whole and bearing on civilian problems, could nonetheless be quickly diverted to war problems.

Yet, as so often happens with any nation that does not make war its business, the scope and organization of this work proved to be inadequate. We have been faced with the urgent necessity of conducting pure research and practical development concomitantly. It is a serious dilemma; we need the research in order to develop the product, and yet, because we *need* the product immediately there is no time for research. We hope that we rationalize the problem, but it is always with us.

One of the very simple problems—simple in the sense that it is easily stated—is palatability. We know that as actually served many dehydrated and compressed foods are less acceptable to the soldier. They also consume more time and care in their preparation than under normal conditions. There is no lunch hour during war, and often we cannot rectify many of the causes of faulty preparation. Since mass feeding with this type of food is new, there is unquestionably much exploration required. What we can solve by more efficient preparation we will; what must be improved within the realm of food chemistry or processing methods must be solved in the laboratory.

A complex problem bordering on pure science is the study of the nutritional requirements of man, particularly under conditions of warfare with which we have no prior normal experience. Fatigue has been a subject of considerable scientific curiosity in the past twenty years. Much outstanding work, for example, has been completed on industrial fatigue. Part of the current problem is discovering and defining whatever analogy exists between war habits and peace habits. While we may know, for instance, what reactions are caused by a given expenditure of energy under given conditions, we then have the problem of reappraising those results in the light of the same energy expenditure under the emotional stress of combat and other completely foreign environmental influences.

Such a subject is susceptible of study, experiment, and final conclusion. Time is, however, the critical controlling factor. We have to reproduce many conditions in the laboratory which require previous experimentation and analysis in the field. After all, while men have flown airplanes all over the world, they have not flown thousands of miles to bomb Tokyo in mass raids. We have no data on which to base inclusive major premises. Likewise people have lived on Guadalcanal for years, but not on reconnaissance missions with con-

current transportation problems of heavy combat equipment and unfamiliarity with living off the land.

It is one thing to feed a man; it is yet another to maximize the safety and efficiency of a soldier through food. We ought to know more about the residual nutritional value of all kinds of processed foods. We ought to know more about the effect of temperature on foods and food values, and about the corrective measures available. Food is a munition and our objective is to maximize its military effectiveness.

No nation can go to war on this unprecedented scale and leave prewar habits untouched. It is good to know that out of this wholesale slaughter will come developments that lengthen human life and make it more enjoyable. It can definitely be said that war development in foods, and the war-accelerated knowledge of nutrition, will cause significant changes in our food consumption habits. A better understanding of the problem of nutrition will be known, and a host of new and better foods will be on the shelves shortly after the war is ended.

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NEW FAT SOLUBLE VITAMIN REPORTED

Since it is now possible to meet the needs of the rat, the standard animal in nutrition studies, with synthetic vitamins, it is natural that investigators turn to other test animals in the search for new dietary essentials. Impetus is given to this urge when it is recalled that the rat does not need a dietary source of several important vitamins such as ascorbic acid, nicotinic acid, biotin, folic acid, and vitamin K, which are essential dietary ingredients for several species. Therefore, interest in the nutritional needs of a fastidious animal such as the guinea pig is increasing. Woolley (*J. Biol. Chem.* **143,** *679 (1942)*) demonstrated that guinea pigs failed to grow or to survive on rations which contained ample amounts of all the known vitamins, and that they needed several additional factors contained in natural foods. Similar observations were reported by Hogan and Hamilton (*J. Nutrition* **23,** *533 (1942)*) and by Sober, Mannering, Cannon, Elvehjem, and Hart (*J. Nutrition* **24,** *503 (1942)*), who concurred in the belief that new dietary essentials could be recognized with the aid of guinea pigs.

In a series of papers beginning in 1936, Wulzen and co-workers at Oregon State College reported a study of a dietary factor which cures a disease of guinea pigs. The last paper by van Wagtendonk and Wulzen (*Arch. Biochem.* **1,** *373 (1943)*) is noteworthy, since it reports the isolation in apparently pure form of a new vitamin which is said to cure the disease.

Van Wagtendonk and Wulzen reported that, when guinea pigs were fed a ration composed of skim milk fortified with skim milk powder, carotene, iron, copper, and orange juice for a month, they developed marked stiffness and finally rigidity of the wrists. Autopsy revealed areas of calcification of soft tissue, such as muscle. This disease was cured within five days by the feeding of raw cream. Pasteurized cream was ineffective because of oxidative changes. The vitamin was fat soluble.

Isolation of the vitamin was accomplished by saponifying the butter prepared from raw cream, steam distilling the fatty acids, separating the active agent in the distillate from acidic compounds, and finally crystallizing it as the mercury iodide complex of a derivative formed with Girard's reagent. The vitamin was recovered from this crystal-

line derivative as a pale yellow oil, which was ten million times more active then the cream from which it came. The overall yield of activity was 60 per cent and must be considered remarkable in view of the lability claimed for the substance. The vitamin is said to be a carbonyl compound with a molecular weight of about 200. Since only 0.1 gamma per day for five days was sufficient to cure a guinea pig of the stiffness of wrist joints, this new vitamin is one of the most active thus far discovered.

Wulzen and Bahrs reported previously (*Am. J. Physiol.* **133,** *500 (1941)*) that the active substance in cream was methyl vinyl ketone. Van Wagtendonk and Wulzen now withdraw this claim, since they have found, as have others, that this ketone not only is not active but is toxic. It is regrettable that little is published regarding the actual data obtained in the quantitative assays. The reader would like to know more about the reliability and reproducibility of the assays, the percentage incidence of the disease, and the adequacy of the basal diet when supplemented with the new vitamin. It is desirable that as much information as possible be available about the biologic test so that more may be learned about this interesting compound. It is difficult to decide if the basal ration was adequately supplied with the known vitamins. Tocopherol could only have been present in minute amounts, and the quantity of orange juice was minimal and may not have been sufficient to prevent the onset of chronic scurvy. Since the symptoms described by van Wagtendonk and Wulzen are similar in many respects to those seen in tocopherol and ascorbic acid deficiencies of guinea pigs, the reader is led to wonder what the effect of feeding adequate amounts of these vitamins would have been. The authors state that wheat germ oil was not active, but apparently they did not test ascorbic acid and a source of tocopherol together. The compound isolated from cream could not have been either of these vitamins.

IRON LOSS BY BLOOD DONORS

Blood donations during the current year will unquestionably reach an all-time high. The American Red Cross has contracted to make 4,000,000 bleedings of 500 ml. each in order to furnish plasma to the American armed forces. Many civilian defense organizations throughout the country are collecting plasma for possible civilian casualties. In addition, hospitals with blood banks are finding that the convenience of the banks has stimulated a greater use of transfusions for their patients. It is safe to assume that donors in the continental United States will be bled to the extent of more than 5,000,000 pints this year. Donors often give blood at intervals of eight weeks for a total of five or six donations per year. Some regular contributors to the Red Cross program have already been bled ten or more times. If this program is viewed in terms of iron metabolism, it will immediately be obvious that an unprecedented drain is being placed on the iron reserves of many people. Furthermore, since so many men have been placed in military service, women are giving more than fifty per cent of the blood being collected. Women are known to have less adequate iron reserves than men because of the demands of menstruation, pregnancy, and lactation.

The influence of this program on iron requirements can be gathered from a few simple calculations. An individual with 12 g. of hemoglobin per 100 ml. of blood (a low normal value) has approximately 40 mg. of iron per 100 ml. of blood. Each time he donates a pint of blood, he loses 200 mg. of iron. This amount is increased to 1 g. or

almost an average of 3 mg. per day if five donations are given in a year. If his diet provides 12 mg. of iron per day, the amount recommended by the Food and Nutrition Board, absorption would have to be 25 per cent complete to compensate for this loss. Assimilation is not likely to be this good. On theoretical grounds, therefore, it would seem that supplemental amounts of iron should be given to "repeating" donors to keep them from becoming iron deficient.

Several observers have reported data which tend to support this idea. Snapper, Liu, Chung, and Yu (*Chinese Med. J.* **56,** *403 (1939)*) observed that Chinese blood donors who subsist on inadequate diets occasionally develop a hypochromic (iron deficiency) anemia. Santy (*Am. J. Med. Sci.* **201,** *790 (1941)*) reported that the rate of hemoglobin regeneration in a group of 27 donors was eight times as fast when they were given 12 grains of ferrous sulfate daily as when no iron was administered. Fowler and Barer (*J. Am. Med. Assn.* **118,** *421 (1942)*) studied hemoglobin regeneration in 200 donors who had given a total of 636 donations. Without supplemental iron, an average of 49.6 days were required for the hemoglobin values to return to the initial level; 25.8 per cent of the donors required more than eight weeks to recover completely. When iron was given in therapeutic amounts to 89 of these subjects, the average recovery period was shortened to 35.2 days and only 6.5 per cent had failed to regain initial hemoglobin values within eight weeks. Iron increased the average daily hemoglobin rise from .0495 g. per 100 ml. blood to .0772 g., an increase of 49 per cent.

Fowler and Barer also noted that when iron salts were continuously administered to repeating donors, the rate of hemoglobin regeneration fell with successive bleedings until it was no greater than it had been without iron therapy. This disturbing result formed the basis for further study by Barer and Fowler in which the phenomenon was again demonstrated (*Am. J. Med. Sci.* **205,** *9 (1943)*). All the subjects were male donors and one gave as many as fifteen pints of blood. Some subjects were given iron continuously while others were treated only after alternate bleedings. The results were always the same. Iron regularly stimulated a faster rate of hemoglobin regeneration following one bleeding but rapidly thereafter lost this effect. Occasionally, it was noted, more rapid hemoglobin synthesis again occurred following the fifth, sixth, or seventh donation, but this was certainly not constant. If it is assumed that the donors had a normal hemoglobin value of 15 g. per 100 ml. and a total blood volume of 5000 ml., the rate of regeneration was rapid enough with iron therapy to replenish the hemoglobin loss within eight weeks except in five instances. The investigators believe that the initial beneficial effect of iron must be one of direct hematopoietic stimulation since there obviously is no great iron depletion induced by the first donation.

There is, therefore, evidence that: (1) hypochromic (iron deficiency) anemia may develop in regular blood donors particularly if their diets are not good, (2) iron initially stimulates more rapid regeneration of hemoglobin after donations, and (3) the effect of iron in producing accelerated regeneration is at least partially lost after several bleedings. This last observation must not be interpreted as indicating that the iron is without effect since depletion of iron reserves is certainly prevented; it merely indicates that hemoglobin formation is no more rapid in people receiving iron regularly than it would be in those same persons with adequate iron reserves.

There is particular need for a study on women donors to determine how imperative it is that they be given supplemental amounts of iron. On theoretical grounds alone, this procedure would seem highly desirable. Cognizance should be taken of the fact that Barer and Fowler, like all other clinical investigators, found no evidence of

bone marrow exhaustion following repeated blood donations.

The importance of nutrition in blood regeneration has been reviewed recently by McKibbin and Stare (*J. Am. Dietet. Assn.* **19,** *331 (1943)*). They mention that good nutrition favors rapid regeneration and that foods rich in iron and protein should be emphasized in the diet of the blood donor. As a measure of safety, the diet should also include liberal amounts of other essentials such as copper as well as those factors whose relation to blood regeneration in man has not been clearly established, such as some of the vitamins of the B-complex. In general, a diet fully meeting the requirements of the Food and Nutrition Board of the National Research Council with increased emphasis on iron and protein foods, can be expected to provide optimum blood regeneration. Specific dietary recommendations for blood donors have been prepared by a committee of the Diet Therapy Section of the American Dietetic Association under the direction of Dorothea Turner, Nutrition Clinic, University of Chicago (*J. Am. Dietet. Assn.* **19,** *336 (1943)*).

NUTRITIVE VALUE OF ENRICHED WHITE FLOUR AND BREAD

It is a curious fact that the enrichment of white flour and white bread was promulgated with little direct experimental evidence to demonstrate the value of such a proposal for the human being. The fact that such evidence now is available justifies the opinions of those persons who had the courage to declare over two years ago that such a step would be desirable on the basis of information then available. As previously reported, analysis of representative foods in the American diet by Lane, Johnson, and Williams (*J. Nutrition* **22,** *613 (1942)*) has shown that the average intake of thiamine of the people in the United States before enriched flour and bread were made available was barely one third of a milligram to each 1000 calories of food. On the basis of a 3000 calorie intake, this would mean that, on the average, people were obtaining just about the minimum requirement of this important dietary factor. The authors calculated that if all the flour consumed were enriched in accordance with the minimum standards proposed at hearings conducted by the Food and Drug Administration, the average thiamine intake would be boosted to 0.5 mg. daily, or just slightly less than the recommended allowance of 0.6 mg., for each 1000 calories, as suggested by the Food and Nutrition Board of the National Research Council.*

Direct evidence of the value of the enrichment of flour now has been provided by Williams, Mason, and Wilder (*J. Am. Med. Assn.* **121,** *943 (1943)*). Their results show that the ingestion of a diet which provided only 0.22 mg. of thiamine for each 1000 calories results after some months in mild thiamine deficiency, whereas the substitution of enriched white flour or whole wheat flour, thus raising the thiamine intake to 0.45 mg. for each 1000 calories, in large measure prevents the development of deficiency signs and symptoms.

The subjects of this study were women volunteers who were carefully selected after preliminary study because of the lack of significant physical or emotional defects, absence of evidence of abnormal nutritive state, and willingness and ability to cooperate. Seven women received the same diet except that two of the subjects received plain nonenriched white flour, and three used flour enriched by the addition of 2.5 mg. of thiamine, 18.0 mg. of niacin, and 27.3 g. of dried skim milk to each pound of flour. The remaining two subjects received whole wheat flour. In every case the amount of flour consumed was about 6 oz.

per day, which represents the average per capita consumption of white flour in the United States. The basal diet is of particular interest. It would appear on the surface as one which was composed of typically "good foods." Each subject received 100 g. of lean beef, or 75 g. of beef plus 35 g. of cottage cheese; from 50 to 75 g. of canned carrots or beets or corn; 30 g. of lettuce or celery; 75 g. of tomatoes or 20 g. of lemon juice; 80 g. of canned pineapple or 100 g. of applesauce or 30 g. of dried, sulfured apricots; 45 g. of butter; 75 g. of cream containing 35 per cent butterfat; 170 g. of flour, which was used in the making of bread, cake, or for other purposes; and 100 g. of sugar, consumed as such or in the form of cake, jelly, or candy. The energy content of these diets was about 2250 calories obtained from 327 g. of carbohydrate, 67 g. of protein, and 75 g. of fat.

All the women were given both physical and neurologic examinations at intervals throughout the study. Determinations were made of the concentration of protein and of calcium and inorganic phosphorus in the blood serum. Determinations also were made of pyruvic acid, lactic acid, and dextrose in the blood after oral administration of dextrose. Determinations of basal metabolic rate were made. Electrocardiograms were taken at intervals. Estimates of gastrointestinal motility following administration of a barium sulfate meal were obtained. The urine was analyzed for its content of thiamine by the thiochrome method under experimental conditions and also following the administration of a number of test doses of 1 mg. of thiamine hydrochloride.

The experiments reported in this account were begun on September 12, 1941 and ended two hundred and sixty-three days later, on May 31, 1942. The two subjects receiving plain nonenriched white flour developed signs, symptoms, and metabolic defects suggesting a thiamine deficiency within one hundred days. These defects were relieved by the administration of thiamine. The two subjects receiving enriched white flour presented no clear signs or symptoms of nutritional deficiency. However, even in these subjects the investigators found evidence that the amount of thiamine was insufficient. This was shown by low excretions of thiamine after test doses of this substance, and also by mild anorexia and subjective symptoms of weakness and irritability. There also were mild elevations of the level of pyruvic acid in the blood after administration of dextrose. The administration of 15 mg. of thiamine hydrochloride daily for two weeks corrected these defects. One of the two subjects receiving whole wheat flour maintained a satisfactory nutritional status, but the other complained of weakness and mild loss of appetite in one hundred days. In the latter subject, the excretion of thiamine in the urine following a test dose, the feeling of numbness and tingling in the medial surfaces of the legs, and the presence of slightly high values of pyruvic acid in the blood after administration of dextrose all indicated that the thiamine intake was not enough to meet the requirement.

The authors also obtained evidence regarding the status of riboflavin in nutrition. For each 1000 calories obtainable from the diets, the subjects receiving the plain white flour obtained about 0.35 mg. of riboflavin, those receiving whole wheat flour or enriched white flour about 0.45 mg. It is to be noted that in all three groups the intake of riboflavin was less than the suggested minimum requirement of approximately 0.67 mg. for each 1000 calories and considerably less than the recommended allowance of 0.88 mg. for each 1000 calories. But the only evidence of riboflavin deficiency observed was a lower excretion following a test dose of 2 mg. of this substance. No abnormalities of the skin, eyes, or tongue, which are characteristic of riboflavin deficiency, developed in any of the subjects. It may be mentioned also that no evidence of niacin deficiency was observed.

The authors concluded that the enrichment of flour with thiamine goes a long way toward correcting the deficiency of thiamine that is apt to occur in the usual selection of foods by the American people. The enrichment of flour with riboflavin up to whole wheat levels, however, did not correct this calculated deficiency in the experimental diets that were used.

It should be pointed out that in these experiments the enriched white flour contained not only added thiamine and niacin, but also dried skim milk to the extent of 6 per cent of the weight of the flour. Not all the flour in the American diet is consumed in the form of bread and not all bread is made with 6 per cent dried skim milk. Indeed, the amount of dried skim milk available is insufficient at the present moment to permit the enrichment of all white pan bakers' bread to this extent. The first order of the Food Administrator required that all white bakers' bread, beginning January 1943, should be enriched with thiamine, niacin, and iron, and also that it contain not more than 2 per cent of shortening, and not less than 3 per cent nor more than 4 per cent (based on the weight of the flour as 100 per cent) of dried skim milk. It has been recommended by the Food and Nutrition Board that, when supplies become available, the amount of dried skim milk in white pan bread be increased to the 6 per cent level. It is generally agreed, however, that dried skim milk should not be obtained at the expense of our present supplies of fluid milk or evaporated milk.

Another point of interest about these experiments at the Mayo Clinic is the observation that signs of thiamine deficiency may appear on a mixed diet that contains as much as 0.45 mg. of thiamine to each 1000 calories. This is in conflict with the experience of other competent investigators. The discrepancy can only be clarified by further study in which perhaps greater control is exercised over the diet as a whole with special reference to riboflavin and the other known dietary essentials. In addition the objective tests of thiamine deficiency need to be subjected to more extensive study before complete reliance can be placed on the results obtained by their use with necessarily limited numbers of human subjects.

VITAMIN SYNTHESIS IN RUMINANTS

The synthesis of any vitamin within the animal body, including the effect of diet change upon the extent of the synthesis, warrants intensive study. In 1928 Bechdel, Honeywell, Dutcher, and Knutsen (*J. Biol. Chem.* **80,** *231 (1928)*) reported that the fermented rumen content of the cow contained more of the vitamin B-complex than could be accounted for on the basis of food eaten. These investigators found that one bacterium, of the genus *Flavobacterium*, was predominant (about 90 per cent) in the rumen microflora and that the feeding of the dead bacteria (from a pure culture) to rats on a vitamin B-complex-free ration resulted in increased growth. Their conclusion from extensive study was that vitamin B resulted from bacterial action, and hence that this phenomenon explained the authors' ability to grow cattle to maturity and have them reproduce on a ration which contained insufficient vitamin B-complex to support growth and well-being in rats.

Other investigators have also reported that certain members of the vitamin B-complex are synthesized in the rumen of the sheep and the cow. Hunt and co-workers (*J. Nutrition* **25,** *207 (1943)*) offer further evidence of the presence and origin of riboflavin and thiamine in the rumen contents of cattle. These authors had previously shown that riboflavin could be synthesized by the cow and had indicated that when the corn content of the ration was the same as the

roughage (by weight), the ration containing whole corn led to less production of riboflavin than the ration containing the same amount of ground corn. In part for confirmation of these findings, they extended their experiments to include studies in which, in addition to the effect of whole versus ground corn, the proportions of hay to corn and increasing amounts of pure carbohydrates in a partially synthetic ration were tried. Steers with artificial rumen fistulas were used. The rations were fed from ten to fourteen days before samples of ingesta were collected. In collecting, the entire rumen content was removed, mixed thoroughly and sampled, and the remainder returned to the rumen. The pH of the rumen content was determined at the time of collection. Rat assay methods and the microbiologic method of Snell and Strong were used in determining riboflavin values.

The results of the experiments indicate that riboflavin is synthesized in the rumen, confirming previous reports. There is also evidence that the kind and physical state of the feed consumed are important factors. The riboflavin content was higher when the corn was ground than when it was whole and as the amount of corn was increased so was the riboflavin level. The corn apparently made a favorable medium by supplying available carbohydrates for bacterial growth. On a corn-free ration (high hay plus protein supplement) there was but little, if any, synthesis of riboflavin. The authors suggest that possibly the increased riboflavin value found when ground corn was fed was due to the greater concentration of water soluble material per gram of dry ingesta.

When, in the partially synthetic ration, the carbohydrate level was varied, it was found that the higher the carbohydrate level of the ration the greater was the amount of riboflavin found in the dried ingesta. Detailed data are listed in seven tables.

The results of the biologic assay (using the rat) and the microbiologic method gave close correlation on the riboflavin values of the feed and ingesta. The data do not show any definite correlation between pH and riboflavin levels.

Hunt *et al.* obtained no evidence that thiamine was synthesized in the rumen as judged by a comparison of feed and the ingesta, with a possible exception of an experiment in which ground corn was fed. McElroy and Goss (*J. Nutrition* **21,** *163 (1941)*), however, reported synthesis of this vitamin and concluded that thiamine, therefore, is not a dietary essential for ruminants. The work of Elvehjem and co-workers also suggests synthetic action. Hunt and associates, in discussing this apparently contradictory evidence, state that their negative evidence does not preclude the synthesis of thiamine in the rumen, since synthesis might occur but escape detection because of rapidity of absorption, destruction, or loss in sampling.

NUTRITION AND RESISTANCE TO INFECTION

The notion that improved nutrition somehow means improved resistance to infection is so attractive and sounds so much like common sense that one finds "most workers are agreed." But agreement, although it engenders felicity, is worthless without a basis in fact. Unfortunately the evidence is lacking, or equivocal at best (*Nutrition Reviews* **1,** *66 (1943)*).

Recently two papers have been presented concerning the influence of nutritive entities on resistance to infection. Decreased resistance due to a dietary deficiency was reported by Trager in a preliminary paper (*Science* **97,** *206 (1943)*). He obtained evidence that biotin deficient chicks and ducks have a decreased resistance to infection by malarial parasites. On the other

hand, an increased resistance due to a dietary deficiency is claimed by Foster, Jones, Henle, and Dorfman (*Proc. Soc. Exp. Biol. Med.* **51,** *215 (1942)*). These workers found that thiamine deficiency in mice increased the resistance to infection with the Lansing strain of murine poliomyelitis virus.

Trager produced biotin deficiency in chicks and ducks by feeding an egg white diet for two to three weeks. Subsequent infection with large doses of *Plasmodium lophurae* resulted in a parasite count 50 to 100 per cent higher, and persistently so, than that exhibited by normal birds similarly infected. This might mean merely that the biotin deficient birds were debilitated in a nonspecific sense. Trager recognized this and showed that in at least one other dietary deficiency, that of pantothenic acid, similar effects were absent. Pantothenic acid deficient chicks and controls showed the same degree of infection. The case for the specificity of biotin was thereby strengthened. Feeding subminimal amounts of biotin, so that growth was good and the only clinical sign was a mild dermatitis, allowed the demonstration of increased infectivity over controls receiving more nearly adequate amounts of biotin. Experiments with another malarial parasite, *Plasmodium Gallinaceum*, yielded similar results.

Trager also found that the biotin levels of red blood cells and plasma rose two or three fold during the course of the infection with *P. lophurae*, and suggests that the rise was connected with the elimination of the parasite. Whether this rise of blood biotin was due to the parasites themselves, or to the massive destruction of red blood cells which occurs during a bout of malarial infection, was not explored. It should be mentioned that the blood biotin levels may be in error as the accuracy of the microbiologic assay for biotin is questionable.

It is unfortunate that little is known about the effects of biotin deficiency, mild or acute, on the hematopoietic system of birds. Since the index of "susceptibility" in Trager's studies, in the last analysis, was based on observation of what was transpiring in the red blood cells, reservation must be made for the possibility that the biotin effects are more directly referable to disturbances in the dynamics of the red blood cell population. In addition it would be well to note that, in spite of our meager information, there is no basis to suppose that our human populations are deficient in biotin in numbers to affect the epidemiologic problem that malaria poses. However, this is all the more reason why work of this kind should be extended so that we may with surety decide which is important, and which trivial.

Foster and associates showed that thiamine deficient mice were more resistant to intracerebral infection with the Lansing strain of murine poliomyelitis virus than litter mate controls which received adequate amounts of thiamine. Further study (*Science* **97,** *207 (1943)*) by the same authors has now shown that simple restriction of stock diet will produce the same effect. Restriction of carbohydrate intake likewise delayed the paralysis and death. The case for the specificity of thiamine is thereby cast in doubt. In general the experiments of these authors are compatible with the claims of virologists that poorly nurtured hosts are infected with more difficulty than well nurtured hosts. Thus Sprunt (*J. Exp. Med.* **75,** *297 (1942)*) found that when food was withheld from rabbits the skin lesions of vaccinia virus were fewer and smaller than in well fed rabbits. All this may be a reflection of the high degree of parasitism exhibited by viruses. The parasitism may be so complete that only a well nurtured cell will suffice as a host.

It may well be that in attempting to define the relation between nutrition and resistance to infection, distinction will have to be made between bacterial infections and virus infections. It is to be hoped that further work will bring clarity to this important problem.

THE METABOLISM OF VITAMIN A

It is generally recognized that the healthy liver is capable of storing and mobilizing large amounts of vitamin A. The findings of McCoord and Luce-Clausen (*J. Nutrition* **7,** *557 (1934)*) and of others, indicate that as long as there is a fair amount of the vitamin in the liver, there is little relation between the blood level of vitamin A and its concentration in the liver. Horton, Murrill, and Curtis (*J. Clin. Invest.* **20,** *387 (1941)*) found however that in rats on deficient diets, the blood and liver levels of vitamin A declined in a parallel manner, indicating that a relationship between the blood level of vitamin A and its concentration in the liver might exist when the liver stores drop below a critical level. Lewis, Bodansky, Falk, and McGuire (*J. Nutrition* **23,** *351 (1942)*) found that the high blood levels resulting from ingestion of large doses of vitamin A were maintained over a long period after discontinuance of the excessive intake. There may well be a degree of liver saturation beyond which the regulatory mechanism for control of the blood level of vitamin A is no longer effective.

Josephs (*Bull. Johns Hopkins Hosp.* **71,** *253 (1942)*) conducted studies on rats which furnish interesting additional information on the relationship between the blood and liver levels of vitamin A and between the serum lipids and the serum vitamin A content. After weaning, rats were placed on a basal deficient diet; one group received in addition 2 to 5 I.U. of vitamin A daily; another, 20 to 100 I.U.; and a third 1000 I.U. or more daily. Some of the animals in each group were killed 24 hours after the last dose of vitamin A, and the content of vitamin A in the serum and liver determined. Others were killed at varying intervals up to about 40 days after discontinuance of the vitamin administration. The author concludes (1) "that the vitamin A tends to be established under the conditions of these experiments at a level of 0.5 to 1.0 units per cc. of serum, and (2) that we may force the level to a higher point by an excessive administration which taxes the ability of the tissues to remove the vitamin from the blood, but that the level falls again relatively rapidly when the excessive administration is discontinued." He considers the serum levels of rats on maintenance and moderate doses as "essentially the same."

The data are however amenable to a somewhat different interpretation. On one chart are plotted the serum values of rats killed 24 hours after the last dose of vitamin A and up to approximately 45 days after weaning. The serum levels of 5 rats on moderate doses and 4 rats on small doses of vitamin A, killed during the first 20 days after weaning, were much the same. However, among the animals killed during the second 25 days or so after weaning, the serum levels of those on small doses ran definitely lower than the levels of those on moderate doses. Only one out of 5 of the animals receiving moderate doses of vitamin A and living longer than 20 days had a serum value as low as 0.75 I.U., while only 2 out of 7 of the animals on small doses had values above 0.75 I.U. The number of animals and the range of serum vitamin A values are too small to permit definite conclusions. The findings suggest first, that under these experimental conditions the serum vitamin A values of rats receiving adequate amounts of the vitamin may tend to be established at a narrow range, and, second, that dosages of 2 to 5 I.U. of vitamin A daily were somewhat less than maintenance. Experiments carried over longer periods of time may show significant differences between the serum levels of rats on small doses and those of rats receiving adequate amounts of vitamin A. In this regard Josephs mentions that "it is possible that with more figures a difference in vitamin A levels in the serum might be established."

The first chart also shows the serum values

of 25 rats maintained on daily doses of 1000 I.U. of vitamin A for periods up to 40 days after weaning. The highest values were found for those animals killed within the first 20 days; 14 out of 17 (82 per cent) had serum vitamin A values of 1.0 units per ml. or above. Of 8 animals killed after 20 days only 3 (36 per cent) had serum levels above 1.0 units per ml. Here again the numbers are small but two probable explanations of this phenomenon, other than the possibility of chance, are worth considering: first, that prolonged administration of large doses of vitamin A increases the ability of the liver to remove this substance from the blood; and second, that as rats grow older the ability of their livers to handle excess amounts of vitamin A increases. As might be expected, the values plotted in the second chart of serum levels of vitamin A at various periods following the discontinuance of larger doses of the vitamin, indicate a considerably more rapid fall than in animals maintained on large doses of vitamin A up until 24 hours before death. This finding suggests that large doses may overtax the ability of the liver to remove the vitamin.

Both the liver concentration and serum level of vitamin A were determined for 59 rats that had been maintained on from 0 to 2000 to 3000 I.U. of vitamin A daily. Thirty-six animals were killed 3 days or more after the last dose of the vitamin, and the serum levels of these rats ranged from 0.5 to 1.0 units, while the range of liver concentrations extended from 3 to 1000 vitamin A I.U. per gram. Below approximately 3 I.U. per gram of liver content, the serum A value drops to very low levels. Only 3 serum values are plotted for liver concentrations between 1000 and 3000 vitamin A I.U., and two of these are above 1.0 I.U. Much higher serum values were found among the rats killed 24 hours after the last dose of vitamin A. In this group the concentration of the vitamin in the liver appears to have had a definite effect upon the serum level. Josephs states that "the most likely explanation for this appears to be that when the concentration in the tissues reaches a high level they become 'saturated' to the extent that they are unable to take up more vitamin A as fast as it comes so that the freshly absorbed vitamin piles up to some extent in the serum." As evidence that this saturation may be only relative, he cites the experience of McCoord and Luce-Clausen, who were able to push the liver vitamin A concentration to extremely high values without demonstrating any influence on serum levels. As previously mentioned, Josephs' own work suggests the possibility that high serum levels 24 hours after the administration of large doses of vitamin A may be a relatively transitory phenomenon, which disappears with continued administration of the vitamin for a long period of time.

Another group of rats was placed on the vitamin A deficient diet (without any vitamin A supplementation) and killed at varying intervals up to 40 to 50 days. The vitamin A content of both the serum and the liver fell rapidly at first, reaching a point close to depletion at about the tenth day. After the twentieth day, no vitamin A was found in either the serum or the liver in any case. Nevertheless clinical evidence of vitamin A deficiency did not occur until the twenty-eighth day at the earliest, and usually somewhat later.

Josephs recognizes the fact that biochemical, physiologic, and perhaps unrecognized anatomic changes may have occurred in his animals long before the accepted clinical signs of vitamin A deficiency became manifest. Partly because of this he conducted some studies on the relation of the serum lipid levels to serum vitamin A levels. In previous clinical studies Josephs (*Bull. Johns Hopkins Hosp.* **65,** *112 (1939)*) found a relationship between total lipid and vitamin A of the serum. When serum lipids were low there was little if any rise in the serum vitamin A after ingestion of large amounts. A significant rise occurred in the postabsorptive vitamin A level only when

the serum lipid levels were within normal limits.

His animal studies demonstrate that (1) serum lipid levels drop significantly below the normal range after about 3 weeks on a basal diet lacking in vitamin A; (2) there is no clear relationship between the fall in serum lipids and the development of clinical deficiency; (3) the decrease in serum lipid values is not due to inanition or to reduction of fat absorption but is "a specific pathological effect of an actual internal deficiency of vitamin A"; (4) liver lipids are reduced during maintenance on a vitamin A deficient diet, but not to nearly the same extent as in other fat depots; (5) the ingestion of large doses of vitamin A by normal rats results in a rise of both serum lipids and vitamin A, followed by a rapid fall to normal; (6) the serum lipid and vitamin A rise which occurs when animals are given large doses of vitamin A is far greater and lasts for a much longer time in deficient than in normal animals; and (7) vitamin A deficiency causes no disturbance in the ability of the liver to store either vitamin A or lipids. The latter fact indicates that the increased and protracted rise of the serum level of vitamin A in the deficient animal is not due to the inability of the liver to remove the vitamin from the blood, nor does it appear to serve any useful purpose, since deficient animals treated with smaller amounts of vitamin A recovered just as quickly without any demonstrated rise above normal in serum vitamin A or lipids. It seems probable that the rise in serum lipids is a specific effect of vitamin A, just as the decrease in serum lipids is attributable to the lack of the vitamin. "The blood lipids act as a vehicle for vitamin A, holding it in the blood so that for a time it may tend to accumulate." No inability of the fat depots to take on lipids was demonstrated in any of the deficient animals.

It is suggested that one function of vitamin A is concerned with lipid metabolism. Perhaps the lipid response to the administration of vitamin A can be developed into a practical physiologic test of vitamin A deficiency in the human subject.

PUBLIC HEALTH APPROACH TO NUTRITION

Some of the difficulties inherent in the evaluation of nutrition surveys have been considered in previous issues of this journal (*Nutrition Reviews* **1,** *45, 72 (1942–43)*). These include the unreliability of dietary histories; variations in standards and in diagnostic criteria; the vagueness of many of the signs and symptoms associated with mild and chronic nutritional deficiencies; and the paucity of satisfactory laboratory procedures, suitable for survey work, for the detection of malnutrition or of inadequate dietary intakes of specific nutrients. The desirability of the adoption, by public health workers in nutrition, of a reasonable amount of uniformity in methods and procedures has been indicated.

Youmans, Patton, and Kern (*Am. J. Pub. Health* **32,** *1371 (1942); Ibid.* **33,** *58 (1943)*) "made a survey of the nutrition of a population with the purpose of developing methods suitable for public health use, demonstrating their effectiveness and securing information as to the nutrition of the group selected."

The authors' description of the reasons for their choice of methods and the detailed account of the procedures themselves merit study by all who are contemplating nutrition surveys of population groups. Briefly, the methods employed consisted of: (1) determination of socio-economic status; (2) a record and study of food consumption on both a household and individual basis; (3) a medical history; (4) a physical examination; and (5) selected laboratory procedures.

The first two articles published by these workers are limited to a general discussion of procedures and the findings in respect to

deficiencies in caloric intake. Presumably it is intended to publish a series of papers, each one dealing with a separate food factor and the methods used for measuring the adequacy of the nutritional status in respect to this factor. Some of the findings and conclusions of Youmans and associates in relation to caloric intake are of sufficient interest, however, to justify reviewing them at this time in advance of publication of the remainder of the material.

The 1152 inhabitants of a small community in Wilson County, Tennessee (91 per cent of the total population) completed the dietary part of the first period of the survey; 85 per cent of the total population also completed the physical and laboratory examinations. Of the total, 33.6 per cent were Negro. Judged by the daily caloric intakes recommended by the Food and Nutrition Board of the National Research Council for various individuals doing different degrees of work, a serious deficiency of calories would appear to have been present in the daily intake of a large proportion of this population.

With the exception of white children from 1 to 6 years of age, all the groups had a caloric intake considerably below the recommended caloric allowance of the Food and Nutrition Board. In some groups the deficiency was as much as 45 per cent. This finding was only partially supported by the existence of a significant degree of underweight in several of the various groups of subjects. Eight of the twenty groups actually had mean weights equal to or greater than the normal. Five of these groups were Negro and in spite of having the lowest caloric intakes were normal with respect to weight. With the caloric deficits indicated, in some groups, one might expect a marked change in strength and a limited activity, but this was not observed.

A 10 per cent sample of the population selected at random revealed that as many as one third of the subjects had a caloric intake less than 30 per cent above basal metabolic requirements, yet their weights ranged from 20 per cent below to 30 per cent above the ideal.

The authors relate other studies of individuals whose intakes were considerably below the usual recommended allowance and yet not associated with a less than ideal body weight. In one instance, a normal 48 year old man of moderate activity apparently consumed a diet providing 2000 calories daily as contrasted to the recommended 3000 calories. Nevertheless his weight was normal; in fact he found it difficult to avoid an increase in weight.

The average daily caloric intake of 1103 male aircraft workers in California investigated by Wiehl (*Milbank Memorial Fund Quart.* **20**, *329 (1942)*) was only 2675 calories, while nearly 40 per cent ingested less than 140 per cent of their estimated basal metabolic requirements.

The collected data therefore indicate that the recommended caloric allowances of the Food and Nutrition Board may be set too high. There would appear to be reason for careful reconsideration of the problem of caloric requirement, particularly the changes in requirements which accompany different degrees of physical activity and the effects of low caloric intake upon individuals within a group whose average intake appears to be satisfactory.

DIETARY FAT AND VITAMIN A ABSORPTION

Since vitamin A is fat soluble, many investigators have suspected that dietary fat may promote its absorption or utilization. Studies of this possible relationship, however, have yielded conflicting data so that there is no real agreement about the role which fat may play in influencing the metabolism of vitamin A. While the fat content

of our diets will probably not be lowered enough, even with the food shortages produced by the present war, to give this question great practical importance, it does have considerable theoretical interest to investigators of nutrition. Muelder and Kelly (*J. Nutrition* **23,** *335* (*1942*)) for instance, have recently determined the effect of different levels of dietary fat on the utilization of graded amounts of vitamin A fed to rats who had previously been depleted of their vitamin A reserves. Rate of growth and incidence of "abscessed" areas (accumulations of keratinized epithelial cells) were the criteria used to measure vitamin A utilization. The basal diet consisted of casein, salt mixture, corn starch, agar, refined cottonseed oil, and bakers' yeast. Cottonseed oil was included at 0, 5, and 10 per cent levels; agar was added to make the three rations isocaloric. Rats were employed in groups of three of the same sex and litter; each member of a triad was fed the 0, 5, or 10 per cent fat diet. Each group of three rats was given the same amount of vitamin A supplement at levels of 0, 1, 3, or 6 I.U. The effect of each amount of vitamin A supplement, therefore, was tested in litter mates of the same sex fed different quantities of fat. The amount of vitamin A given was found to be a more important factor in promoting weight gain than was the level of dietary fat, but in all instances, except those in which the animals received no vitamin A, there was some weight gain and it was best with the 10 per cent fat diet. This last observation was interpreted as indicating that fat aided the absorption of vitamin A. Growth in length of the animals and incidence of "abscesses" were favorably influenced by vitamin A but not affected by the fat content. These results would indicate that while vitamin A absorption is aided by dietary fat, its utilization after assimilation has occurred is independent of the fat.

Somewhat different conclusions were reached by Russell, Taylor, Walker, and Polskin (*J. Nutrition* **24,** *199* (*1942*)), who studied the absorption and retention of carotene and vitamin A in hens maintained on diets of normal and low fat content. These workers found that the level of dietary fat did not influence vitamin A absorption, but their low fat diets contained 0.07 per cent fat, and an additional 1 mg. of corn oil was fed with each 200 I.U. of vitamin A. The effect of this small amount of fat could not be evaluated, but it may have favored absorption. The technic of measuring absorption was essentially that of a balance study. After these absorption measurements had been completed, the hens were maintained on their respective rations without vitamin A supplement for one month and then killed. The amount of vitamin A found in the livers of the normal diet group was 37 per cent of the total amount administered, while only 4.9 per cent was found in the livers of the hens fed the low fat ration. This result would seem to cast doubt on the accuracy of the absorption data, but the authors cite unpublished work to indicate that the difference in liver vitamin A was probably caused by greater retention of this factor by the "normal ration" hens during a depletion period which preceded the absorption studies. The authors did not include direct evidence that hens on the normal fat diet really had retained significant amounts of vitamin A in their livers at the time the absorption study periods began. In the second part of their study, these workers demonstrated that in hens the absorption of carotene fed in crystalline form is improved by the presence of fat in the ration.

The fact that investigators have not been able to reach an agreement about the influence of dietary fat on vitamin A absorption is an indication, obviously, that the problem is not easy to solve. How complicated it may be, and how rigidly the diet may have to be controlled is indicated by the demonstration of Adlersberg and Sobotka (*J. Nutrition* **25,** *255* (*1943*)) that defatted commercial lecithin greatly improves vitamin A absorption, even in patients with sprue.

PATHOLOGIC CHANGES IN VITAMIN C DEFICIENCY

The primary morphologic effects of vitamin C deficiency were shown by Wolbach and Howe (*Arch. Path.* **1,** *1 (1926)*) and others to occur in the intercellular substance of certain mesenchymal derivatives. Hemorrhages, loosening of the teeth, failure of wounds to heal and, in infants, extensive subperiosteal hemorrhages and separation of the epiphyses of long bones are manifestations of scurvy which are readily explained by a defect in the formation and maintenance of intercellular materials. The mechanism by which ascorbic acid promotes the formation of collagenous intercellular substances is not known but it can be suspected that it is concerned with the chemical mechanisms of cells responsible for the synthesis of the protein, collagen. The relationship of ascorbic acid to protein metabolism is indicated also by the observations of Levine, Gordon, and Marples (*J. Clin. Invest.* **20,** *209 (1941)*) who described a spontaneous defect in the metabolism of aromatic amino acids in infants fed cow's milk containing 5 g. or more of protein per day. In the urine of such infants 1-p-hydroxyphenyllactic and p-hydroxyphenylpyruvic acid were excreted. The administration of ascorbic acid completely eradicated the defect. These observations indicate that ascorbic acid is concerned in the metabolism of tyrosine and phenylalanine.

Heretofore cytologic studies in ascorbic acid deficiency have revealed no changes of importance in epithelial organs except perhaps in the skin where the keratosis of the hair follicles may possibly be due specifically to lack of ascorbic acid (Crandon, Lund, and Dill, *New Engl. J. Med.* **223,** *353 (1940)*). Evidence of pathologic changes in the parenchymal cells of the liver and in the proximal convoluted tubules of the kidney of scorbutic guinea pigs is presented in the recent report of Russell and Callaway (*Arch. Path.* **35,** *546 (1943)*).

Four groups of animals were used: guinea pigs fed a ration deficient in ascorbic acid; guinea pigs fed the same ration but supplemented with lettuce ad libitum; an inanition group given lettuce but none of the basal diet and so controlled that their weight loss was as great as that of the scorbutic animals; and a group fed the scorbutic diet supplemented by daily intraperitoneal injections of ascorbic acid. To all of these animals trypan blue was given subcutaneously in a 1 per cent concentration in physiologic solution of sodium chloride. The injections were commenced on the fourteenth day of the experiment, at the time when the animals receiving the vitamin C-deficient diets began to show the first symptoms of scurvy. The amount of dye given in each instance was adjusted to the size of the animal. All the animals in a group, with the corresponding control animals, were killed after the first spontaneous death occurred in a scorbutic animal of that group. Blocks of the tissues were fixed in formaldehyde, and paraffin sections were prepared and stained lightly with trinitrophenol. This made it possible to see the trypan blue easily in the sections.

Russell and Callaway found considerably more trypan blue in the sections of liver and kidney from the scorbutic animals than in those from the corresponding control animals. The dye was observed as minute granules indiscriminately placed throughout the cytoplasm of the liver cells. As would be expected, the Kupffer cells were filled with the dye both in the scorbutic and in the control animals. In addition to these changes, moderate to advanced fatty degeneration of the liver cells, particularly in the region of the central veins, was observed. In the kidneys the dye was observed in the cytoplasm of the cells of the proximal convoluted tubules in all the animals but those of the scorbutic animals contained "unmistakably larger amounts." Arguing that trypan blue has a strong affinity for all pathologically altered and dead tissues, the

authors conclude that vitamin C deficiency produces a pathologic change in the cells of the liver and kidneys of the guinea pig.

The study of pathologic alterations by a method which depends on the deposition of a dye is fraught with difficulties. Furthermore, fatty changes in the liver have been observed experimentally in a number of different types of deficiency. It is to be noted that the authors depended on "rabbit chow checkers," their basal diet, to supply the vitamins of the B-complex. Their study would have been more valuable if the B-complex factors had been deliberately added. Nevertheless the observations are of interest since they suggest pathologic changes in organs not commonly considered as associated with the defects caused by lack of vitamin C. Since the liver is concerned in protein metabolism the studies are of special interest in view of the possible relationship of ascorbic acid to protein metabolism as discussed already. The findings in the kidneys are of interest because of the report that alkaptonuria following the administration of *l*-tyrosine to guinea pigs is closely correlated with the amount of vitamin C given such animals (Sealock and Silberstein, *Science* **90,** *517 (1939)*).

A better understanding of the pathologic changes observable in the ends of the growing bones of scorbutic infants or experimental animals is found in the experiments of Follis (*Arch. Path.* **35,** *579 (1943)*). That some of the changes regarded as characteristic of scurvy are attributable to the effects of stress and strain has long been assumed. Follis put the matter to test. In a series of guinea pigs receiving a scorbutogenic diet, a narrow plaster bandage was wound about one of the hind legs, beginning at the ankle and extending to include part of the abdomen. In this way one hind leg was almost completely immobilized while the opposite one was allowed freedom of motion. Groups of the animals were killed at intervals and the histologic pictures of the lower ends of the femurs and the upper ends of the tibias of the free and immobilized legs were compared.

There was a striking difference in the histologic appearance of the bones of the two limbs. In bones that had been immobilized a broad "lattice" of calcified cartilaginous matrix, wider than normal, was present but this "lattice" was not being destroyed. On those portions of the "lattice" where osteoid should have been, no osteoid deposit was present. In the marrow spaces there was extensive erythropoietic and myeloid activity, and fractures of the "lattice," so characteristic of the classic picture of scurvy, were absent. Furthermore, there was no proliferation of connective tissue cells nor any pink-staining "fibrin-like" material or hemorrhage. In the bones of the free limbs this pink-staining substance was accumulated about the points of fracture, hemorrhages were present, and marrow cells were not found at the cartilage-shaft junction.

It is clear that pathologists have learned to identify scurvy in bones by the secondary changes to which lack of ascorbic acid leads rather than by the primary histologic defect, which is the cessation of osteoblastic activity, as indicated by a failure to destroy the calcified cartilaginous matrix (the "lattice") and to form osteoid. In fact the primary alterations in the absence of those produced by stress and strain, Follis implies, are not sufficiently specific to permit the histologic recognition of vitamin C deficiency in bones.

THE RELIABILITY OF FOOD TABLES

Widdowson and McCance have taken time out, so to speak, from their many recent metabolic studies to discuss the value and some of the limitations in the use of food tables in nutritional studies (*Lancet* **I,** *230 (1943)*). They have shown experimentally

that for most of the dietary essentials the actual composition of diets is closely approximated by the values obtained through the use of suitable food tables, with the exception of the values for calcium and iron. Even in the case of these elements, they have found the discrepancy not as great as that which has been reported by a number of American investigators. They have demonstrated that the values for protein, fat, potassium, magnesium, and phosphorus can be estimated with considerable precision by the use of a balance for weighing out samples of food and by calculations made with the aid of food tables.

In one series of experiments involving 6 persons over a period of one week, the average calcium intake by analysis was 4.68 g., by calculation 4.11 g.; the average iron intake was 65.0 mg. by analysis and 61.6 mg. by calculation. It is to be noted that the actual values for both calcium and iron were higher than those obtained by calculation. The tendency in the United States has been for investigators to find that the actual values by analysis for these elements are usually lower than the calculated values. The discrepancy in iron intake in the British experiments under discussion was attributed to the use of curry in seasoning of the fish which was included in the diet, curry powder being known to contain a relatively large and variable amount of iron. The calcium intake was consistently higher than that calculated in the case of each subject and this was considered to be owing to the fact that the food was prepared with the use of tap water. In other experiments where distilled water was used, not only for drinking but also for cooking, and where no curry was eaten, the average iron intake for one week for 8 subjects was 173 mg. by analysis and 187 mg. by calculation, which shows excellent agreement. In the case of calcium in this series of experiments, the actual intake was 3.95 g. per week and by calculation 3.98 g.

There is thus considerable support for the view of these authors that food tables may be used with a great deal of accuracy in estimating dietary intakes. As they have pointed out, there have been two extreme schools of thought about food tables: "One tends to regard the figures in them as having the accuracy of atomic weight determinations; the other dismisses them as valueless on the ground that a foodstuff may be so modified by the soil, the season or its rate of growth that no figure can be a reliable guide to its composition. The truth, of course, lies somewhere between these points of view."

In many dietary surveys no account has been taken of the calcium content of drinking water and sometimes the amount supplied in this form may be appreciable. Widdowson and McCance estimate that in regions where the drinking water is hard, British people may secure nearly 200 mg. of calcium daily from this source. In other regions, of course, where the drinking water is soft, the calcium contribution of the water will be considerably less. Vegetables which are cooked in hard water may absorb calcium. Potatoes boiled in distilled water were found to contain 4.71 mg. of calcium to each 100 g. and, when boiled in Cambridge tap water, which is of moderate hardness and contains about 5 mg. of calcium to each 100 ml., they contained 6.69 mg. When boiled in Cambridge tap water to which a little table salt (containing 3.29 mg. of calcium to each 100 g.) had been added, the potatoes contained 9.28 mg. in each 100 g. Similar results were obtained in the cooking of peas, the values being respectively 22.4, 38.9, and 44.9 mg. to each 100 g., when cooked in distilled water, tap water, and tap water containing salt which, in turn, contained calcium salts. It is apparent, however, that the amounts of calcium obtained in this way are small as compared to those which might be obtained from the drinking water.

Contamination of foods with iron may be of considerable magnitude, as all chemists

who have worked with the traces of this element present in foods are aware. Experimentally the British investigators found that apples contained 0.31 mg. of iron to each 100 g. when cut with a stainless steel knife and cooked in distilled water in a glass beaker. When the apples were cut with an ordinary kitchen knife and then cooked in distilled water in a glass beaker, the iron content was 2.3 mg. to each 100 g.; and when cut with an ordinary knife and cooked in distilled water in a chipped enamel pan, the iron content was 6.0 mg. to each 100 g. Thus, stewed apples when prepared and cooked in this common manner became "as good a source of iron as the best roast beef." Most vegetables do not take up iron to this extent, perhaps because they are less acid in reaction. Apparently the organic acids of fruits, especially malic and citric acids, are responsible for the solvent action. But iron contamination is not limited to fruits. In some additional experiments, raw lean beefsteak which contained 2.73 mg. of iron to each 100 g., was found after mincing to contain 4.79 mg. Thus it is apparent that the values for iron intakes are apt to be actually ihgher than those calculated from tables of food analysis. Such iron from the wearing of metal utensils is probably metallic and available to the human organism, in the opinion of Nakamura and Mitchell (*J. Nutrition* **25,** *39 (1943)*). These Illinois investigators recently reported some experimental results in which they found whole corn to contain 3.5 mg. of iron in each 100 g. but, after putting through a cutting (Wiley) mill, the meal contained 6.1 mg. If ground in a burr mill the iron content was increased to 12.5 mg. to each 100 g. No doubt the wearing of pots and pans and kitchen cutlery has to a large measure been responsible for an appreciable amount of the iron which people have received in their foods.

VITAMIN E AND MUSCLE PHYSIOLOGY

Evans and Burr in 1928 first called attention to the muscle paralysis which occurs in the suckling rats of vitamin E deficient mothers. Since then lesions have been demonstrated in young guinea pigs, rabbits, ducklings, hamsters, and in older rats on vitamin E deficient diets. Tocopherol is effective in preventing or curing this disorder and numerous chemical changes associated with the degeneration have been noted. In the muscle there is a decreased content of creatine, glycogen, acid-soluble phosphorus, phosphocreatine phosphorus, potassium, and magnesium. An increase in cholesterol, sodium chloride, and calcium may be found, but the various chemical changes do not necessarily parallel each other. In rabbits a large increase in creatine excretion occurs and the urinary creatine-creatinine ratio has in fact been suggested to indicate the onset and severity of the dystrophy.

The demonstration of thiamine, nicotinic acid, and riboflavin as components of oxidative enzyme systems represented in each instance a most fundamental advance in the physiology of these vitamins. In a series of recent papers Houchin and Mattill have demonstrated the significant effects of the lack of vitamin E on the oxygen consumption of the dystrophic muscle and an effect of tocopherol phosphate on such muscle *in vitro*. These changes suggest that this vitamin also plays a role in the regulation of oxidative processes in muscle.

In their first paper of the series these authors (*J. Biol. Chem.* **146,** *301 (1942)*) described their technic for the production of muscle dystrophy and the results of measurements of the oxygen consumption of normal and dystrophic muscle. Both low and high fat diets were used, but the former produced the most consistent and rapid production of muscle dystrophy. This diet

contained the following percentages of constituents· cellophane 20, casein 15, sucrose 10, starch 36, lard 3, cod liver oil 3, yeast 10, and salt mixture 3. On this diet rabbits weighing 500 to 850 g. developed dystrophy in two and one-half to five weeks and the Syrian hamster showed a severe dystrophy in two to four weeks. The semitendinosus and sometimes the gastrocnemius muscle, after being sliced lengthwise, were used for measurement of oxygen consumption by the usual Warburg technic.

The average oxygen consumption of the muscle of 5 normal rabbits was 1.4 cmm. oxygen per mg. of dry weight per hour, while the average of 12 dystrophic muscles was 3.12. In the hamster a similar large increase occurred, amounting to 250 per cent of normal. A decrease in creatine and a great increase in sodium chloride content of the muscle also occurred. Animals receiving vitamin E but the same diet showed a normal muscle oxygen consumption.

The response of the muscle to administration of tocopherol or its acetate to the animal appears to be rapid and dramatic. In hamsters the abnormally high oxygen consumption of the muscle dropped to normal in twenty-seven hours after administration of 1 mg. of α-tocopherol. To make the point more certain, biopsy experiments were performed on rabbits so that the oxygen consumption of the muscles of the same animal could be measured before and after tocopherol administration. In these experiments a 28 to 43 per cent reduction in muscle oxygen consumption occurred in 10 to 48 hours after α-tocopherol acetate administration. Operation or anesthesia had no effect on the muscle oxygen consumption. The authors concluded that the return toward a normal rate of oxidation in muscle is the primary result of the feeding of tocopherol.

This phase of the work was further studied (*J. Biol. Chem.* **146,** *309 (1942)*) by administration of the more soluble α-tocopherol phosphate by ear vein. In this case, again by the biopsy technic, an average reduction of 33 per cent in the muscle oxygen consumption occurred within the short period of one hour, and an ever greater change after three to four hours. In similar experiments on normal animals, including the injection of α-tocopherol phosphate, no change was noted. The authors concluded that the more rapid response was due to the immediate availability of the soluble tocopherol phosphate.

Houchin (*J. Biol. Chem.* **146,** *313 (1942)*) then studied the *in vitro* effect of α-tocopherol phosphate. It was found that the oxygen consumption of muscle from vitamin E deficient rabbits and hamsters in a medium containing 5 mg. per cent of α-tocopherol phosphate averaged 40 per cent less than slices of the same muscle in an unsupplemented medium. As a control, it was noted that when the oxygen consumption of the muscle had already been reduced by administration of tocopherol to the animal, no further effect of tocopherol phosphate was found. Muscle from abnormal animals was likewise unaffected by vitamin E *in vitro.*

In contrast to the muscle slices, a mince or homogenate of muscle gave nearly identical oxygen consumption values for both normal and dystrophic muscle. For reasons based on this fact and because of the simplicity of the operations, the ability of the muscle homogenates to oxidize the metabolite succinic acid was studied. The succinic acid oxidizing power of dystrophic hamster muscle was 160 per cent above that of normal muscle, and again the addition of α-tocopherol phosphate caused a marked diminution of this oxidation. The author concluded that the vitamin "could hardly be effective in any other way than as a chemical regulator of the succinoxidase system."

In this connection it may be recalled that Stare, Gordon, and Musser (*Nature* **141,** *831 1938*)) found a *less* active succinic acid oxidation system in biopsy samples of muscle from clinical patients with various myopathies. No inference was made, however, that a lack of vitamin E was related to the human

myopathies examined. Although it is true that there are reports of clinical improvement of certain muscular dystrophies upon administration of this vitamin, there are also many negative reports. As yet there is no proof that vitamin E deficiencies occur in man, or that muscle dystrophies in man are related to vitamin E.

The observations of Houchin and Mattill are of great significance to the understanding of the physiologic function of vitamin E. If vitamin E acts as a catalytic agent in muscle oxidations, it would logically be expected that a muscle lacking in this factor would show an abnormally low respiration. Actually a great increase in respiration was found by Houchin and Mattill. However, too little is known about the control of oxidative processes, or even the succinoxidase enzyme system, to make this consideration a valid objection to the hypothesis that vitamin E may act as a catalytic agent in tissue oxidation. In this connection it is of interest that vitamin C deficient guinea pig tissues show an increased oxygen uptake and that the liver of riboflavin deficient rats has also been shown to have an increased respiration, although not of the order of magnitude found for vitamin E deficient muscle. Actually the authors have postulated that the presence of α-tocopherol hinders chemical changes within the succin-oxidase system, so that in its absence the oxidative processes "run riot." The antioxidant properties of α-tocopherol are well recognized but virtually nothing is known of the effect of this class of substances on physiologic oxidative processes. The rapid effect of α-tocopherol phosphate given intravenously or added to vitamin E deficient muscle *in vitro* might even suggest a nonspecific antioxidant action except for the fact that no effect could be observed on normal muscle. The possibility that a vitamin might act as an inhibiting principle in contrast to the positive catalytic action of some other vitamins is an interesting suggestion in the field of biologic oxidation.

FOODS THAT DISAGREE WITH HEALTHY PEOPLE

The question of digestive disturbances resulting from food is of interest to both the nutritionist and the physician concerned with planning either normal or therapeutic diets. Food prejudices are common; many people have peculiar ideas about what they can or cannot eat—ideas which may or may not rest upon fact.

In 1935 Alvarez published data compiled from interviews with 500 patients of the Mayo Clinic in which he had collected information regarding the foods which disagreed with them. All subjects had come to the clinic for medical advice, hence were not in normal health. A surprisingly long list of foods appeared to cause discomfort in one way or another. However, this may be expected when health is below par.

Hughes (*J. Am. Dietet. Assn.* **12,** *314 (1936)*) reported the findings on 1000 healthy adults. Six hundred of the subjects were college women with an average age of 20 years, the second group consisted of 200 men and 200 women from 30 to 65 years of age. All were in "good" or "excellent" health. The type and extent of reactions to a large number of foods—belching, nausea, headache, distention, regurgitation, vomiting, pain, and urticaria—are listed in tabular form for the two age groups. For both groups raw onion proved to be the chief offender; approximately one quarter of the subjects reacted to this food with four or more symptoms. Radishes and cooked cabbage were second, affecting roughly 16 per cent of the group; beans were third, producing reactions in some 14 per cent; the other foods were listed as distressing less than 10 per cent of the subjects. The younger group, in general, had a some-

what higher reaction percentage. Thirty-nine per cent in this group reported distress from a single food, and in the older age group 44 per cent were upset by only one food. It was interesting that foods which frequently cause allergic reactions such as chocolate, pork, sea food, and milk were near the bottom of the list.

There was a marked difference in response to raw and cooked cabbage. For the younger group the incidence of distress following the eating of cooked cabbage was 14.7 and for the raw cabbage 3.7 per cent. The opposite effect was noticed for raw and cooked onions. Raw onions produced disagreeable reactions in one fourth of the individuals but when they were cooked only 3 per cent of the adults and 9 per cent of the college group were affected. The differences must be explainable on a basis of the chemical reactions which occur during cooking. The sulfur compounds in uncooked cabbage are apparently less irritating than the decomposition products formed under the influence of heat. The longer cabbage is cooked the greater the accumulation of irritating products. With onions, however, there is a loss of irritating substances upon cooking.

Inasmuch as some individuals stated that the greatest discomfort arose when cabbage was much overcooked, and others that the disturbing symptoms were greater when the cabbage was cooked in a covered kettle, the effect of cooking seemed worthy of consideration. This was the subject of a second report by Hughes and Campbell (*J. Am. Dietet. Assn.* **15,** *24 (1939)*).

The volatile sulfur compounds are found in plants as glucosides which decompose on boiling. Starting vegetables to cook in cold or tepid water permits plant enzymes to decompose the sulfur compounds before the enzymes are destroyed by heat. It also prolongs the cooking time. Retention of volatile acids, by covering the kettle, favors the decomposition of the sulfur compounds. The strong flavor of old cabbage, cauliflower, and turnips is thought to be due to the setting free of sulfur compounds by enzymatic action.

In this second experiment 20 healthy subjects (20 to 25 years of age) were chosen. All were known to suffer gastrointestinal disturbances when cabbage was eaten but none had manifest symptoms of allergy. Cauliflower and cabbage, both raw and cooked, were tested under various conditions. The vegetables cooked for one and a half hours were the worst offenders, next was the raw cauliflower, then the coarsely shredded cabbage, the vegetables cooked forty-five minutes, the finely shredded raw cabbage, and least disturbing of all were the vegetables cooked only until tender.

Recently Hughes and Harris (*J. Am. Dietet. Assn.* **18,** *815 (1942)*) studied the influence of the method of preparation on the disturbing effects of onions. Raw onions had been found to be from three to seven times more upsetting than cooked onions. As in the previous study only subjects known to suffer discomfort upon eating onions were chosen. Ninety-two per cent reported discomfort when the onions were eaten raw, 87 per cent when they were vinegar soaked, 67 per cent reacted to those cooked in a closed kettle, but only 42 per cent when the kettle was left uncovered even though the cooking time was the same. The best method was found to be that of cooking only until tender. With this method 80 per cent could tolerate the onions without ill effect. Gas and belching were the most generally reported symptoms.

These findings, coupled with studies on the effect of cooking on the nutritive value, indicate the importance of the time factor in food preparation and the need for intelligent choice of method for the preparation of specific foods. In the program of national food economy, as well as that limited to the home, preparation of food assumes a place of greater importance than has been generally conceded to it.

THE CHOLINE CONTENT OF ANIMAL AND PLANT PRODUCTS

With the acceptance of choline as an important dietary factor, accurate information as to its distribution becomes desirable. Until recently the data which were available had been determined by biologic assay. Fletcher and co-workers in 1935 and Jukes in 1941 reported values for a number of foods using this method. The chemical method for determining total choline described by Engel (*J. Biol. Chem.* **144,** *701 (1942)*) is a further step in the accumulation of source and potency data. The procedure in this method consists of extracting the material with absolute methanol, reducing the extract to near dryness, hydrolyzing the residue with boiling aqueous barium hydroxide, neutralizing with acetic acid, and finally precipitating the choline at 3°C. by the addition of reinecke salt. Using this method, Engel has reported values on a hundred animal and plant products (*J. Nutrition* **25,** *441 (1943)*).

Of the animal products, egg yolk was found to be the richest source of choline. Visceral organs, heart, and nervous tissue were among the best animal tissue sources. The choline contents of the organs in all mammalian species examined were uniform and related to their phospholipid content. Only traces of choline were found in butter and lard. The choline content of skim milk powder was nearly one-third greater than that of the whole milk, indicating, as one might expect, that the choline was not in the fatty portion. It is known that the lecithin in milk is closely associated with the proteins.

In cereal grains the choline is concentrated in the germ. Removing the germ from corn, for example, resulted in a choline loss of 75 per cent. In the manufacture of white flour there was a 50 per cent decrease in choline. Wheat shorts and wheat bran are considerably better sources of choline than the whole grain cereal.

Cottonseed meal, soybean meal, and peanut meal were equal or superior to the respective whole kernels as sources of choline. In the commercial extraction of oil from these materials the amount of choline removed is proportional to the total solids extracted. Refined vegetable oils are practically devoid of choline. In general the seeds and seed meals are better sources of choline than the cereal grains. It had been reported by MacLean and MacLean in 1927, that seeds which are low in protein contain less phospholipids than seeds which are relatively high. The choline distribution supports this suggestion.

Green leafy vegetables and vegetable legumes are better sources than the grain seeds or vegetable root crops, and on a dry basis are equivalent to muscular tissue as sources of choline.

Some of the values reported by Engel are, in milligrams per gram: egg yolk 17, beef liver 6.3, beef kidney 3.3, turnips 0.94, polished rice 0.94, and cheddar cheese, 0.48.

Rhian, Evans, and St. John (*J. Nutrition* **25,** *1 (1943)*) using first the method of Jacobi, Bauman, and Meek (*J. Biol. Chem.* **138,** *571 (1941)*) and later the method of Engel, determined the "choline content of feeds." In all cases higher values were obtained by the Engel method. (Engel had found methyl alcohol to be a more satisfactory solvent than the alcohol-ether mixture used by Jacobi *et al.*) Comparative values by the two methods were given. These authors conclude that the cereal grains are poor sources of choline, animal products such as liver and fish meals are good sources, while soybean oil meal and meat meals have intermediate values.

Elvehjem (*J. Am. Dietet. Assn.* **18,** *145 (1942)*) in discussing meat in its relation to human health, also lists some choline values. Those given, without reference to the analytical method employed, are definitely lower than the values reported by Engel, but here again liver and kidney are reported as rich sources.

AVIDIN AND OVARIAN FUNCTION

Avidin, a protein substance found in raw egg white, occupies a unique position in nutrition. By combining with biotin in the intestinal tract it prevents the absorption of this vitamin, and hence causes, when fed in sufficient amounts to animals, a biotin deficiency. No similar substances are known. The reason for the presence of avidin in egg white remains a mystery although Hertz and Sebrell (*Science* **96,** *257 (1942)*) have suggested that, since it has been found in the albuminous portion of all fowl eggs tested and in the egg jelly of frogs, it may play an important role in embryonic development and in the physiology of the genital tract. Most important advances in our knowledge about avidin are the recent demonstrations that avidin arises as a secretory product of the mucosa of the oviduct of birds and that its formation is related to ovarian function (Fraps, Hertz, and Sebrell, *Proc. Soc. Exp. Biol. Med.* **52,** *140 (1943)*).

Fraps and associates assayed various portions of the oviduct of laying hens as well as oviducal and freshly layed eggs for their avidin content. Their method of assay was based on the inhibition of growth of a strain of yeast which multiplies at a rate proportional to the concentration of available biotin in the culture medium. One unit of avidin is required to inhibit completely the yeast growth supported by 1 microgram of biotin. It was found that avidin was present in the magnum (albumen-secreting portion) of the oviduct of laying hens in amounts ranging from one to five units per gram of fresh tissue but could not be detected in the isthmus or uterus. When an autopsied hen was found to have an oviducal egg in the magnum, the titer of the tissue was greater below than above the level of the egg. This differential was interpreted as indicating that the portion of the magnum from which albumen had already been secreted had discharged a part, but in no case all, of its avidin content. Avidin was present in the magnum following lay but prior to subsequent ovulation; the presence of an egg in the oviduct, therefore, is not a condition necessary for the presence of avidin. The albumen of eggs, like the tissue of the magnum itself, contained 1 to 5 units of avidin per gram. Lastly, all portions of the oviduct, including the magnum, of nonlaying hens was void of any avidin. The conclusion is drawn from these data that avidin formation or secretion by the albumen-secreting portion of the oviduct is dependent, either directly or indirectly, on the complete reproductive function of the ovary.

The same group of investigators reasoned that if avidin production is related to ovarian function, its formation might be stimulated artificially in sexually immature or nonlaying hens by ovarian hormones (Hertz, Fraps, and Sebrell, *Proc. Soc. Exp. Biol. Med.* **52,** *142 (1943)*). Consequently they treated 142 immature chickens and 35 hens, who had terminated their laying season, with stilbestrol, progesterone, or a combination of the two. In every instance, injections of stilbestrol followed by progesterone induced formation of avidin by the magnum. In contrast, however, progesterone by itself was without this effect, and only an occasional bird treated with stilbestrol alone showed avidin in its magnum. The reason for the irregular response to stilbestrol was not known.

These researches have defined the tissue source of avidin and have related its formation to ovarian activity. They add more weight to the suggestion that the avidin-biotin complex is important in the physiology of avian reproduction.

MYOCARDIAL NECROSIS IN THIAMINE DEFICIENCY

The human disorder beriberi is classically known as consisting of two main forms—the "wet" type and the "dry." The former is characterized by edema and signs of heart failure. The "dry" form is marked by paralytic symptoms.

Pathologic observations in human beriberi have not been satisfactory. In the "wet" type particularly, pathologic studies have for the most part been limited to gross examination of the heart, and few detailed microscopic studies have been made. Wenckebach ("Das Beriberi-Herz," *Julius Springer, Berlin, (1934)*) described "hydropic" degeneration of the myocardial fibers, but Weiss and Wilkins (*Ann. Int. Med.* **11,** *104 (1937–38)*) found the same change in other types of heart disease as well, and Wilkins and Cullen (*J. Clin. Invest.* **12,** *1063 (1933)*) found an increase in the water content of the myocardium of both ventricles in the hearts of patients dying of congestive failure of various types.

Attempts to reproduce the syndrome of beriberi have heretofore been made largely by feeding animals autoclaved yeast. Such studies have been made chiefly in pigeons, but other animals including dogs, rats, and pigs have been studied to some extent. In only a few of the experiments reported have specific lesions of the myocardium been described, and these reports have appeared only recently. Swank (*J. Exp. Med.* **71,** *683 (1940)*) observed scattered foci of necrotic muscle fibers in pigeons, and this worker together with Porter and Yeomans (*Am. Heart J.* **22,** *154 (1941)*) reported small scattered foci of necrotic muscle fibers in 3 out of 14 dogs. Van Etten, Ellis, and Madsen (*J. Nutrition* **20,** *607 (1940)*) found scattered areas of "atrophy and necrosis" of heart muscle fibers in 7 pigs fed a diet supplemented with sulfite-treated liver and whey. It is noteworthy also that in foxes dying of Chastek paralysis, a disorder which has been attributed to thiamine deficiency, Evans, Carson, and Green (*Am. J. Path.* **18,** *79 (1942)*) also described areas of necrosis of myocardial fibers.

Much more pronounced changes in the heart than have been described are reported in pigs by Follis, Miller, Wintrobe, and Stein (*Am. J. Path.* **19,** *341 (1943)*). It is to be noted that these workers did not depend on autoclaved yeast for the production of a deficient diet because, as they point out, autoclaving may destroy more than thiamine. They gave as the only source of the vitamin B-complex a mixture of crystalline vitamins which included riboflavin, nicotinic acid, pyridoxine, choline, and calcium pantothenate. Three animals were given no thiamine whatever and 3 others received 10 micrograms of thiamine hydrochloride per kilogram of body weight per day. A third group of animals received no crystalline vitamins, but were fed 1.5 g. of desiccated whole liver per kilogram of body weight per day.

Striking changes in the cardiovascular system developed. Four animals, which had shown nothing more than some impairment of appetite and of growth, died quite unexpectedly. Two animals were observed to develop labored breathing and cyanosis which were made much worse by exercise. One of these animals died after induced exercise. Three animals were killed.

In all the animals except those killed, pronounced changes in the myocardium were observed. These consisted of areas of focal or diffuse necrosis, some of which were infiltrated by leucocytes and, in the more chronic cases, were replaced by connective tissue cells so that scars resulted. The lesions in one instance were so great that they could be detected grossly. The hearts showed well-pronounced dilatation, although the evidence of actual muscular hypertrophy was not conclusive. In a pig which died early in the experiment, lesions were confined to the auricles, but in those dying later, lesions were noted both in the

auricles and in the ventricles. In no instances were pathologic changes found in the ventricles when they were lacking in the auricles. This indication that the auricles may be more sensitive to thiamine deficiency than the ventricles is of interest in relation to the observation by Muus, Weiss, and Hastings (*J. Biol. Chem.* **129,** *303 (1939)*) who noted that there was a reduction from normal in the oxygen consumption of the auricular muscle *in vitro* in thiamine-deficient rats, while that of the ventricles remained unchanged. In the animals which were killed, no myocardial lesions were observed. These animals had been receiving thiamine in doses sufficient to reduce the pyruvic acid of the blood to normal levels for the preceding thirty to forty-five days.

The myocardiums of 45 pigs which had died of deficiencies other than thiamine or which had received all of the crystalline vitamins of the B-group, were examined and failed to show the myocardial necrosis described in thiamine-deficient animals. It is to be noted that a number of these animals had failed to grow normally and that two were pigs whose food had been purposely restricted in order to study the effect of chronic inanition on the tissues. The myocardial lesions cannot therefore be attributed simply to inanition.

This report brings convincing evidence of the important role of thiamine in maintaining the integrity of the heart muscle. In view of the well-recognized role of thiamine in carbohydrate metabolism, the observations recorded are, however, not surprising. They show clearly how a biochemical defect may lead to profound histologic changes.

It will be necessary to examine carefully the hearts of patients dying as the result of nutritional deficiency in order to see whether lesions similar to those observed in pigs will be found in man. As already stated, the studies in man hitherto recorded have scarcely been adequate enough to indicate whether similar lesions are likely to be found. It is to be noted that pathologists have observed and reported from time to time cases of unexplained myocarditis associated with heart failure in which the changes were strikingly similar to those now reported in thiamine deficiency. It will be interesting to see whether directed observations will reveal evidence of thiamine deficiency in some of the cases of unexplained myocarditis.

It is also to be noted that Follis, Miller, Wintrobe, and Stein were unable to find changes in the nervous system in any of the animals, and did not find evidence of degeneration of the vagus nerves. Degeneration of the vagus nerves was at one time considered to be a cause of the cardiac manifestations of human beriberi. The paralysis observed in beriberi has also been attributed to thiamine deficiency. Views as to whether thiamine deficiency is responsible for nerve degeneration in man have been largely gained by inference from animal experimentation. Questions of species differences, time for development of the deficiency, as well as the type of diet all appear to be factors leading to differences of opinion in this matter (*Nutrition Reviews* **1,** *252 (1943)*). Certainly on the basis of present knowledge concerning the distribution of vitamins in food, beriberi would be expected to be a multiple deficiency syndrome resulting from the lack of more than one vitamin. While it appears that the cardiac manifestations of this disorder may be due to lack of thiamine, other symptoms may be due to deficiencies in other substances.

MORE ABOUT NUTRITION IN INDUSTRY

An interesting series of articles on health problems in industry has been presented in a recent issue of the Journal of the American Medical Association, this being part of the report of the Fifth Annual Congress on Industrial Health which was held in Chicago in January, 1943. Approximately four hundred industrial physicians and surgeons, nurses, manufacturers, nutritionists, and others interested in problems of nutrition in industry took part in a three day program. Among some of the trends of the day reflected by the reports is a consideration of women in industry and the special problems of a medical nature which are thereby presented. Carlson (*J. Am. Med. Assn.* **121,** *806* (*1943*)) contributed a virile article about the older worker in which he points out, among other things, that the older person should not be relegated to a career of inactivity but should be permitted to perform work that fits his capacity, if necessary at a lower stipend. Keefer (*J. Am. Med. Assn.* **121,** *802* (*1943*)) discussed the control of the common cold and other respiratory infections. In harmony with the views of others who have given thoughtful study to the evidence, Keefer concludes that the use of cold vaccines has been disappointing. Likewise, large doses of vitamins A, B_1, B_2, C, and D and nicotinic acid, or vitamin C alone, had no significant effect on either the number or severity of upper respiratory infections when administered to young adults who are already consuming a reasonably adequate diet.

One of three articles in a symposium on nutritional problems of industry deals with the criteria for the evaluation of nutrition experience in industry. In this report Bing (*J. Am. Med. Assn.* **121,** *813* (*1943*)) suggests that applied nutrition is a health problem and that the proper measure of dietary adjustments is to be sought in the body of the workman—in the field of pathology and physiology and medicine—rather than in the observation of secondary effects which may be controlled by many factors other than the diet. The necessity for controlled studies in the field of nutritional investigation is particularly emphasized.

Government activity in connection with industrial nutrition, reviewed by Goodhart (*J. Am. Med. Assn.* **121,** *823* (*1943*)), is exemplified by the establishment of a section on Nutrition in Industry in the Nutrition and Food Conservation Branch of the Food Distribution Administration. This section functions primarily through the eleven regional nutrition representatives and the state and local nutrition committees throughout the United States. Thus the problems of nutrition in industry and the improvement of the nutritional status of workers is an integral part of the National Nutrition Program. Further, the section has an arrangement with the Industrial Hygiene Division of the U. S. Public Health Service and the ordnance branch of the United States Army whereby an inspection of meals, feeding conditions, and requirements is to be included in the industrial hygiene surveys of army ordnance plants. Through liaison with the Public Health Service there is a close relationship with the various state industrial hygiene departments. Some of the features of the activities of this department are described, and Goodhart urges industry to call on the state and local nutrition committees for the services they are prepared to give. In a previous review in this journal (*Nutrition Reviews* **1,** *70* (*1943*)) the opinion was expressed that "cooperation with established, reliable agencies that are actively interested in better nutrition probably would repay the management of many war industries."

Cowgill (*J. Am. Med. Assn.* **121,** *817* (*1943*)) has collected and reviewed information on current nutritional activity

in industry, and has emphasized the need for improving plant facilities for the feeding of workers. Many industrial organizations are cooperating in the field of education regarding foods and nutrition, best known perhaps being the activities of the Westinghouse Electric and Manufacturing Company, the General Electric Company, and Servel, Inc. "To the extent," writes Cowgill, "that a firm participates in this international effort through any of the many ways open to it, to that extent it can be sure that its employees have learned how to secure their own health through the proper use of food, and how they can help to win the war through the best possible use of our national food resources."

In a round table discussion of these reports, a number of persons interested in the subject took part under the chairmanship of J. S. McLester. The leaders included L. B. Pett of Ottawa, Ontario, George R. Cowgill, Russell M. Wilder and L. D. Bristol. Pett made the observation, in reply to a query, that a survey of foods eaten by workers is essential prior to an educational program on nutrition because it will permit recommendations about improvement in the diet to be made in such a way as to influence as little as possible the food habits on the people. Wilder presented an opinion on a number of questions involving a consideration of carbohydrate metabolism. He believes that a tendency to develop low blood sugar values between meals may be a reason for the consumption of carbohydrate-rich foods at those times. At first such a practice may produce some feeling of relief, but ultimately the habit is likely to lead to an increased sensitivity to fatigue, because the underlying cause is neglected. In well recognized cases of hypoglycemia, it has been found that the preferred method of treatment is to place such persons on a high-protein, high-fat diet with restriction of carbohydrate, especially of sugar. To eat a good breakfast and an adequate lunch, it is believed, will help prevent that type of weakness so prominent at about 11 a.m. and 4 p.m.

It is Wilder's opinion that the satisfactory breakfast should contribute a good share of the day's nutritive requirements. Vitamin C and some carbohydrate may be supplied in the form of a fruit juice, B-complex vitamins by a satisfactory portion of whole grain cereal, breakfast food, or bread. Butter or properly enriched oleomargarine supplies some fat which by delaying the emptying of the stomach contributes to a satisfied feeling for a longer time. The value of drinking whole milk cannot be overemphasized. An egg or equivalent quantity of meat is most desirable for a breakfast.

The remaining discussion and the nature of the questions from the audience indicates the active interest that industrial physicians are developing in the field of nutrition, an attitude a previous report (*Nutrition Reviews* **1,** *151* (*1943*)) suggested to be highly desirable. Further information concerning the activities of the American Medical Association in this important field may be obtained by writing to the Secretaries of the Council on Foods and Nutrition or the Council on Industrial Health, 535 N. Dearborn Street, Chicago.

DIETARY INADEQUACIES AMONG CHILDREN

A health survey by the Elizabeth McCormick Memorial gives added proof of the urgent need for improvement of the nutrition and food habits of the American people. Hardy and associates (*J. Am. Dietet. Assn.* **19,** *173* (*1943*)) report the second half of this survey. The first part, on the physical fitness of children from different economic levels, was reported earlier (*J. Am. Med. Assn.* **117,** *2154* (*1941*)). The survey ex-

tended over two and a half years and included 7363 children (2 to 18 years of age) from 3922 families representing different national and racial groups and a wide distribution of economic and social conditions from 45 different neighborhoods scattered over the city of Chicago. Physical examinations, medical histories, and individual diet records served as the sources of the data presented. The authors recognized the fact that there are no specific physical signs which are diagnostic of early nutritional failure; however, when certain conditions occur in combination, they seem highly suggestive of an unsatisfactory nutritional state. Among these physical signs they list dental caries, bad posture, round shoulders, poor muscle tone, insufficient subcutaneous fat, poor color, rachitic chest abnormalities, bowlegs, certain skin abnormalities, and flat feet. Exclusive of dental abnormalities, only 14 per cent of the children were free from all such defects. Sixty per cent were found to have two or more undesirable characteristics, in addition to caries, and as many as seven occurred in 8 per cent of the children; for example, 45 per cent had abnormalities of the extremities; 44 per cent, bad posture; 34 per cent, rachitic chest deformities; 26 per cent, poor muscle tone; 26 per cent, deficient fatty tissue; 20 per cent showed definite pallor. Both singly and in combination, signs of nutritional deficiencies occurred more frequently among the Negro than among either the white or Mexican children; 17 per cent of Negro children showed seven or more defects, in contrast to 6 per cent of the white and 4 per cent of the Mexicans. Throughout there was a consistent and direct association of physical condition with the socio-economic class. The differences were large and statistically significant.

Inasmuch as food consumption and nutritional status are unquestionably related, the diet patterns of the children were investigated. A record was made of the variety of food eaten and the number of times each type of food was served to the child—whether raw, cooked, or in combination with other foods. In the hands of skilful interviewers this method of ascertaining food intake may be considered reasonably satisfactory. Diet patterns were accepted as meeting the minimum standards if the weekly consumption included 5½ quarts of milk, 24 servings of fruits and vegetables including potatoes, and 7 servings of meat, fish, poultry, and eggs.

Among the 7363 children studied only 28 per cent met this minimum standard. Of these, 11 per cent were Negro, 7 per cent Mexican, 41 per cent of native parentage, 27 per cent had one foreign born parent, and 25 per cent were of foreign parentage. The dietary inadequacies were common among children of all ages. Even among children whose parents were financially able to provide adequate diets, at least one third of the diets were classed as inadequate.

In the course of this study the use of food stamps by relief clients offered the opportunity to see what effect an increase in the food budget would have on the diet pattern. Definite improvement was noted. There was an increase in "good" diets from 5 to 25 per cent among native born whites, 2 to 14 per cent among those born of foreign parents, and 3 to 23 per cent for the Negro children. But it is significant that under the stamp plan an average of only 20 per cent of the diets became "good," while 23 per cent remained "poor."

The consumption of protective foods was evaluated six months later and the findings are presented in tabular form. It is shown that the protein foods were least frequently low and that fruits and vegetables were most frequently consumed in unsatisfactory amounts.

The survey presents evidence of the considerable amount of malnutrition existing among children. This is associated with the economic level of the family to a large extent, but it is also greatly dependent upon dietary knowledge and food habits. Community programs for health improvement should be both intensive and extensive.

NOTES

Food Problem Fundamentals

"Here are some of the facts I hope every American will keep before him as he thinks about food and acts to produce it, save it, share it, use it wisely, and adjust his habits to the changes of war time.

1. Food doesn't just happen; it can't just be taken for granted. Food has to be produced by work and planning and conserved by genius and care.

2. Our allies actually do depend in large measure on the food supply from which we eat so freely and the success of the RAF and the Russian army are a part of our direct responsibility in food management.

3. Our armed forces must plan with a margin of safety and for rapid replacement of supplies that are sunk at sea. The army is prudent in its takings of food.

4. The civilian supply of food will be large enough for health and strength for all, but not for waste.

5. Rationing of some foods is necessary; it is difficult to administer a rationing program perfectly, but some rationing system must be relied upon to assure fairness in dividing the supply among all; without it there would certainly be less fairness.

6. Never during the war, no matter how long it lasts or how wise and skilled we become—never will we get all the problems solved and all the difficulties overcome. Never during this war can the consumer or producer settle down to assurance that all the food producing and food using habits can stay the same from here on out. There can be no such hope. He must expect change, which is inherent in war. Neither the production nor the needs can be completely prophesied. The only thing constant about war is that there will always be change.

Citizens must know the vital importance of food in the war. They must understand the total food program. They must know the increase that could be made in the effective food supply if waste could be eliminated. They must know the cumulative effect on the usefulness of food as a weapon if each individual played his full part." (From an address by former War Food Administrator Chester C. Davis at the Dairymen's League Co-operative Association annual meeting in New York City, N. Y., June 17, 1943.)

Vitamins in Rose Hips

Much attention has been given to the rose hip as a potent source of vitamin C. In addition to the 1200 to 1500 mg. of ascorbic acid per 100 g. that they contain, they also appear to contain carotene equivalent to some 6000 to 10,000 I.U. of vitamin A per 100 g. They thus have a vitamin A value similar to that of carrots.

Food Habits and Food Values

In their classic study, "The Physique and Health of Two African Tribes," J. B. Orr and J. L. Gilks found the diet of the Kikuyu to be particularly poor in calcium. The Kikuyu are an agricultural tribe subsisting mainly on a vegetarian diet excessively rich in carbohydrate and strongly deficient in protein. Protein deficiency is probably the world's major nutrition problem and characterizes the diets of all poor populations, such as India, China, or Africa. The Kikuyu eat meat rarely and drink little milk, which in addition is forbidden to females from puberty to menopause. Their staple is millet, to which maize has been recently added. Orr and Gilks found the population to possess acute calcium deficiency.

In a subsequent study of the diet of another African tribe to the south, the Bemba, which subsists also on a vegetarian diet with millet as a staple, no calcium deficiency was found (A. I. Richards *et al.*).

The diets of the two tribes are almost identical, yet the Bemba diet "contained more than twice as much calcium as the average English diet" and the physique of this tribe was superior to that of the Kikuyu. The reasons for this discrepancy were clarified by analyses which showed that the millet eaten by the Kikuyu was white millet containing 0.020 per cent calcium, while the variety eaten by the Bemba was finger millet containing 0.320 per cent calcium. This difference may be genetic or it may be determined by soil and climatic conditions. The latter is doubtful and the result is probably the product of both sets of factors.

Another reason for the inferiority of the Kikuyu diet and health was the increasing use of maize, which contains only 0.005 per cent calcium. Hence just as one must have luck to be born into let us say a democracy rather than a caste society, so one must have a lucky star to direct one into a society that by chance, choice, or necessity became attached to a staple properly endowed by nature. Can science master this dictatorship of chance and offer mankind sound nutritional guidance and practices?

Vitamin C and Potatoes

Potatoes are not a particularly rich source of vitamin C but because they are such a staple commodity and eaten in such quantity they do in some circumstances contribute materially to the vitamin C supply. The food cooking principles illustrated in the study on potatoes by Jenkins (*Nature* **151,** *473 (1943)*) can furthermore be extended to other vegetables which may be richer in vitamin C.

The whole boiled potato contained 5.4 mg. of ascorbic acid per 100 g. If kept hot, 45 per cent of the ascorbic acid remained at the end of twenty minutes, and only 17 per cent after one hundred thirty-five minutes. In contrast, when the cooked potato stood at room temperature, it retained 80 per cent after one hundred thirty-five minutes.

The loss of vitamin C from the mashed potato is particularly great. Twenty minutes standing caused a loss of nearly two thirds of the original vitamin C content, and in thirty minutes only 10 per cent remained.

The common restaurant practice of keeping vegetables hot for long periods, although convenient, obviously produces increased losses of vitamin C and probably other factors. In the case of potatoes, it is obviously preferable to mash just before consumption. These principles should be recognized both in communal feedings and in the home.

A New Dehydrated Soup

The Agricultural Research Administration in cooperation with members of the food industry recently announced the development of a dehydrated soup made of pea meal, soybean grits, and dry skim milk. The mixture is precooked so that it can be prepared for serving quickly by adding the dry soup mix to cold water and bringing it to a boil. In 1941 about 5 million pounds of dry pea soup were purchased by the Agricultural Marketing Administration for its school lunch program, and the newer product is likely to be used even more extensively, not only for school lunches but also for Lend-Lease purposes.

Recent Nutrition Books

Vitamins and Hormones. Vol. I. Advances in Research and Applications. Edited by Robert S. Harris and Kenneth V. Thimann with a foreword by E. V. McCollum. Academic Press Inc., N. Y. 1943. pp. 413.

The Science of Nutrition. Henry C. Sherman. Columbia University Press, New York. 1943. pp. 253.